REMARKS

Status of the Claims

Claims 1-11, 19, 22, and 23-26 are pending in the present application. Claims 27-29 have been added. Support for these claims can be found in the specification, for example, in Example 8. No new matter has been added by way of this amendment.

The Examiner is respectfully requested to withdraw the rejection and allow claims 1-11, 19, 22, and 23-26 and not apply them to new claims 27-29. In any event, the Examiner is requested to enter the above amendments for purposes of furthering prosecution. These amendments were not made earlier because Applicant earnestly believes that the specification is enabling for the breadth of the claims as originally drafted. Reconsideration and reexamination is respectfully requested in view of the following remarks.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Enablement

The Examiner rejected claims 1-11, 19 and 22-26 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable one skilled in the art to make or use the invention. The Examiner asserts that the specification, while enabling for nucleic acids encoding SEQ ID NO:3 or 5, host cells, plants, plant cells and seeds comprising them, and a method of using them to make SEQ ID NO:3 or 5, does not reasonably provide enablement for methods and compositions drawn to nucleic acids encoding pesticidal proteins with 90% or 95% sequence identity to SEQ ID NO:3 or 5, nucleic acids with 90% or 95% identity to SEQ ID NO:1, 2, or 4, or host cells, plants, plant cells and seeds comprising them, and a method of using them to make a pesticidal protein with 90% or 95% identity to SEQ ID NO:1, 2 or 4. The Examiner states that the specification fails to provide guidance for which amino acids of SEQ ID NO:3 or 5 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of the encoded protein, as well as which regions of the protein can tolerate insertions and still produce a functional protein. This rejection is respectfully traversed for the reasons of record which will not be repeated in their entirety herein.

Instead, Applicants direct the Examiner's attention to *Ex parte Kubin*, 83 USPQ2d 1410 (Board of Patent Appeals and Interferences 2007). The claim at issue in *Kubin* was:

> 73. An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having at least 80% identical [sic] to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48. *Ex parte Kubin* at page 1412 (emphasis added).

In concluding that the above claim was fully enabled, the Board remarked that the "*Wands* factors weigh in Appellants' favor, particularly 'the state of the art' and 'the relative skill in the art,' as evidenced by the prior art and Appellants' specification. *Ex parte Kubin* at page 1416 (internal citation omitted). Furthermore, the Board stated that "[t]he experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine," and "[t]he techniques necessary to do so were well known to those skilled in the art." *Id.*

In the present case, the claims are drawn to an isolated nucleic acid molecule comprising a nucleotide sequence having at least 90% or 95% sequence identity to SEQ ID NO:1, 2, or 4, or encoding a polypeptide having at least 90% or 95% sequence identity to SEQ ID NO:3 or 5, wherein the encoded polypeptide maintains pesticidal activity. Accordingly, the variant pesticidal sequences are on point with the variant sequences of *Kubin*, in which the Board concluded that the claims were fully enabled, particularly in view of the *Wands* factors of the state of the art and the high level of skill of those in the art. Moreover, as in the *Kubin* application, the present specification teaches in detail how to: 1) make variants of the relevant sequences and calculate the percent identity between the original sequence and the variant sequence (see, for example, pages 8-13); and 2) assay for pesticidal activity (page 8, lines 25-29 and Examples 7 and 8). See *Ex parte Kubin* at page 1415. The Board concluded in *Kubin* that a sequence having *only* at least 80% sequence identity to a disclosed sequence and the functional limitation of being able bind CD48 was fully enabled. Here, Applicants are claiming a nucleotide sequence comprising a sequence having at least 90% sequence identity to SEQ ID

NO:1, 2, or 4, wherein the sequence encodes a polypeptide having pesticidal activity. Applicants note that the recited limitation of 90% sequence identity is significantly higher than the 80% sequence identity limitation that the Board deemed fully enabled in the *Kubin* decision.

Furthermore, the Examiner's enablement rejection on grounds that the specification only provides guidance for polypeptides that are toxic to lepidopteran species rather than a broader genus of pest as described in the specification is improper. In so arguing, the Examiner appears to imply that the specification must demonstrate activity against every pest that could be used in the invention. However, the Federal Circuit has held "[t]he enablement requirement is met if the description enables *any* mode of making and using the claimed invention." *Engel Industries Inc. v. The Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991) (emphasis added). Applicants' specification clearly meets the enablement standard set forth in *Engel* with regard to the pending claims because the knowledge in the art and the specification provide sufficient guidance to enable one of skill in the art to make and use the claimed compositions (e.g., nucleotide sequences encoding polypeptides that are pesticidal).

The Examiner alleges that there appears to be a conflict between the claims' recitation of "pesticidal activity" due to the specification's very broad definition of pests and the specification's indication that variant proteins should have the same pesticidal activity as the original protein. However, the specification states that the variant protein have a particular level (e.g., at least about 30%) of activity, not a particular type of activity. Thus, the term "pesticidal activity" is not limited to the particular species against which the parent sequence has demonstrated activity. Nonetheless, claims 27-29 have been added which specify that the variant polypeptides have lepidopteran activity. Limitation of these claims to lepidopteran activity is not intended to exclude variants which also have activity against pests other than lepidoptera.
The Examiner also contends that, while much is known about the structure of Cry proteins, relatively little is known about the structures responsible for function. The Examiner points to a passage one page 187, column 2 of Bravo and Soberon ((2005) *Comprehensive Molecular Insect Science* 6:172-205, Gilbert *et al.*, Ed., Elsevier Ltd, Oxford, UK) in making this assertion. However, this particular passage and the various cited references describing the structure/function relationship of individual domain II loops to insect specificity confirms the

role of domain II in receptor recognition and binding.

The Examiner also relies on the teachings of Jones *et al.* (2007) *FASEB J.* 21:4112-4120 in concluding that little is known about the structure/function relationship of delta-endotoxins. However, Figure 3 indicates that Jones *et al.* were able to align Cry49Aa with other binary proteins, identify conserved residues and blocks of conserved sequences amongst this class of proteins (i.e., characterize the structure), and deduce the function of Cry49Aa as a binary protein based on this alignment. The authors state on page 4118, column 1, paragraph 1, that "[a]n alignment of these protein sequences (Fig. 3) indicates that the blocks of the conserved sequence, previously noted between BinA and BinB proteins [], are also well conserved throughout this whole family of proteins."

The Examiner also continues to rely on the teachings of de Maagd *et al.* (1999) *Appl. Environ. Microbiol.* 65:4369-4374, Aaronson *et al.* (2001) *FEMS Microbiol. Lett.* 195:1-8, de Maagd *et al.* (2001) *Trends Genet.* 17:193-199, Tounsi *et al.* (2003) *J. Appl. Microbiol.* 95:23-28, Angsuthanasombat *et al.* (2001) *Biochemistry Molecular Biol.* 402-407, and Guo *et al.* (2004) *Proc. Natl. Acad. Sci. USA* 101:9205-9210 in asserting the unpredictability in making substitutions in a *cry* protein. Although some mutations may result in an unpredictable change in the activity or function of a particular protein, the majority of the art that is specific to delta-endotoxins discusses the significant structure/function relationships determined for this particular class of proteins.

In light of the above arguments as well as those previously made of record, the level of skill and knowledge in the art, and the guidance provided in the specification, Applicants respectfully submit that the specification is enabling for the full scope of claims 1-11, 19, and 22-26. Thus, the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn and not applied to new claims 27-29.

Written Description

Claims 1-11, 19, 22 and 23-26 were further rejected under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. The rejection is respectfully traversed.

The Examiner asserts that the disclosure is insufficient to support claims that are drawn to a genus of nucleic acids having 90% or 95% sequence identity to SEQ ID NO:1, 2, or 4, or nucleic acids encoding polypeptides having 90% or 95% identity to SEQ ID NO:3 or 5.

In order to satisfy the written description requirement of 35 U.S.C. § 112, the application must reasonably convey to one skilled in the art that the applicant was in possession of the claimed subject matter at the time the application was filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). Every species encompassed by the claimed invention, however, need not be disclosed in the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). The Federal Circuit has made it clear that sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharm L.P. v. Faulding In.*, 230 F.3d 1320 1323, 596 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims.").

Moreover, the "Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement" state that a genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics , *i.e.* structure or other physical and/or chemical properties." *Id.* at 1106. This is in accordance with the standard for written description set forth in *Regents of the University of California v. Eli Lilly & Co*, 119 F.3d 1559 (Fed. Cir. 1997), where the court held that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name' of the claimed subject matter sufficient to distinguish it from other materials." 119 F.3d at 1568, citing *Fiers v. Revel* 984 F.2d 1164 (Fed. Cir. 1993). In *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.2d 926 (Fed. Cir. 2002), the Federal Circuit adopted the PTO standard for written description, stating:

> [U]nder the Guidelines, the written description requirement would be met . . . if the functional characteristics of [a genus of polypeptides] were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt

> the PTO's applicable standard for determining compliance with the written description requirement."

The claims of the present application meet the requirements for written description set forth by the Federal Circuit. The claims as amended recite that the nucleic acid have at least 90% or 95% sequence identity to the nucleotide sequence of SEQ ID NO:1, 2, or 4, or to a nucleotide sequence encoding SEQ ID NO:3 or 5. Methods for determining percent identity between any two sequences are known in the art and are provided in the specification. See pages 8-13. As discussed above, nucleotide sequences for full-length AXMI-014 (SEQ ID NO:1), as well as variants and fragments (e.g., SEQ ID NO:2 and 4) are disclosed in the specification. Numerous delta-endotoxin sequences were also generally known in the art at the time the application was filed. Moreover, detailed information regarding the structure of delta-endotoxins and the reported functions associated with particular structures, regions, and motifs was also available in the prior art as well as discussed in detail on page 2, lines 22-29, Figure legend 1, and on pages 12-13.

At the time of filing, it was known that delta-endotoxins generally comprise three domains, a seven-helix bundle that is involved in pore formation, a three-sheet domain that has been implicated in receptor recognition, and a beta-sandwich motif. See Li *et al.* (1991) *Nature* 305:815-821. Thus, the recitation of polypeptides having a particular percent identity to a delta-endotoxin provides very specific and defined structural parameters of the sequences that can be used in the invention. These structural limitations are sufficient to distinguish the nucleotide and amino acid sequences of the invention from other nucleic acids and polypeptides and thus sufficiently define the genus of sequences useful in the practice of the present invention.

The Examiner maintains that the specification describes no relevant characteristics or motifs for the claimed nucleic acids other than identity to SEQ ID NO:1, 2, or 4, and that the structures associated with the disclosed function are not known or described in the specification. Applicants respectfully disagree with the assertion that no relevant characteristics or motifs were disclosed. As discussed above, domains associated with specific functions were known (Li *et al.*, *supra*), and conserved regions within each of these functional domains are described in the specification. Li *et al.* state that the overall structure of this delta-endotoxin represents the

general fold of the family of active delta-endotoxin proteins (see the abstract of Li *et al.*), and that the core of the cry3Aa molecule is built from the five sequence blocks that are highly conserved throughout the delta-endotoxin family (column 2, page 817 of Li *et al.*). Four of these highly conserved sequence domains have been described in the instant specification as they relate to the delta-endotoxin of the invention.

The Examiner is also reminded that the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2000). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). Here, Applicants have provided nucleotide and amino acid sequences for exemplary pesticidal sequences and variants and fragments thereof encompassed by the claims. Moreover, numerous delta-endotoxin sequences were known and readily available in the art. The Examiner states that the claims are not limited to Cry proteins. However, the sequences disclosed in the instant specification share common motifs and function as Cry proteins, and the information regarding these motifs can be applied to sequences sharing at least 90% or 95% sequence identity to SEQ ID NO:1, 2, or 4 of the present invention. Therefore, Applicants submit that in view of the present disclosure and the knowledge and level of skill in the art the skilled artisan would envision the claimed invention.

The description of a claimed genus can be by structure, formula, chemical name, or physical properties. *See Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), *citing Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). A genus of polypeptides may therefore be described by means of a recitation of a representative number of amino acid sequences that fall within the scope of the genus, *or* by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *See Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); *see also* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2000). The recitation of a predictable

structure (i.e., an amino acid sequence having a specified percent identity or number of contiguous amino acid residues of a particular sequence) is sufficient to satisfy the written description requirement. Thus, the application provides the structural features that characterize sequences having at least 90% or 95% sequence identity to SEQ ID NO:1, 2, or 4, or to a nucleotide sequence encoding SEQ ID NO:3 or 5 that retain pesticidal activity.

An Applicant may also rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the sequences recited in the claims. *Id.*, citing *Lilly* at 1568. The present claims further recite functional characteristics that distinguish the sequences of the claimed genus. Specifically, the claims as amended recite that the sequences having at least 90% or 95% sequence identity to SEQ ID NO:1, 2, or 4, or to a nucleotide sequence encoding SEQ ID NO:3 or 5 encode proteins which have pesticidal activity. The specification and the art provide standard assays that may be used to measure pesticidal activity. See, for example, page 8, lines 27-31. Furthermore, as noted above, Applicants have disclosed fragment sequences that retain pesticidal activity (e.g., SEQ ID NO:4, which encodes a fragment of SEQ ID NO:3). Accordingly, both the structural and functional properties that characterize the genus of sequences that can be used to practice the invention are specifically recited in the claims. The sequences that fall within the scope of the claims can readily be identified by the methods set forth in the specification.

In summary, the specification provides an adequate written description of the claimed invention. In particular, the specification provides: nucleotide and amino acid sequences for pesticidal toxins, and variants and fragments thereof, that fall within the scope of the claims; guidance regarding sequence alterations that do not disrupt pesticidal activity of a toxin; guidance for determining percent identity; and methods for assaying the pesticidal activity of proteins. In view of the above remarks and claim amendments, Applicants submit that the relevant identifying structural and functional properties of the genus of sequences of the present invention would be clearly recognized by one of skill in the art. Consequently, Applicants were in possession of the invention at the time the application was filed, and the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of written description should be withdrawn.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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